REVIEW

Mechanism of bariatric and metabolic surgery: beyond surgeons, gastroenterologists and endocrinologists

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ABSTRACT

Bariatric-metabolic surgery is the safest, most effective and long-lasting treatment for obesity and its associated co-morbidities, whether they be metabolic (type 2 diabetes, hyperlipidemia non-alcoholic fatty liver disease) or cardiovascular (myocardial infarction, stroke). Due to the obesity pandemic, bariatric-metabolic surgery is the second most frequent intra-abdominal procedure and the gastroenterologist and the surgeon must be aware of the physiologic changes caused by the anatomic reconfiguration following surgery.

Among the mechanisms of action, independent of the loss of weight and fat tissue, surgery leads to the release of gut hormones related to carbohydrate metabolism (the rapid and continuous release of insulin), appetite and degree of satiety (glucagon-like peptide 1, peptide Y-Y, grhelin). As a result, indications for surgery have been extended to earlier disease stages. Apart from the neurohormonal effects, changes in the metabolism of biliary acids and the microbiota have also been reported.

The aim of this review is to describe the physiologic changes caused by bariatric-metabolic surgery.

Keywords: Bariatric surgery. Metabolic surgery. Inflammation. Diabetes type-2. Pathophysiology. Incretins.

INTRODUCTION

Over the last 40 years, one of the most striking changes in the human phenotype has occurred with catastrophic repercussions on health as a consequence of the progressive increased incidence of overweight and obesity in adult and child populations (1). According to the World Health Organization (WHO), in 2015 there were more than 603.7 million obese adults and 107.7 million obese children. The prevalence of childhood obesity (< 5 years) is estimated to be 41 million and continues to increase. In 2013, the American Medical Association (AMA) recognized obesity as a medical illness with genetic and epigenetic origins (1).

In Spain, the prevalence of overweight in adults is estimated to be 39.4 % (46.4 % in males and 32.5 % in females) and that of obesity is 22.9 % (22.4 % in males and 21.4 % in females (2). The WHO defines obesity as an excessive increase in fat accumulation, which leads to pathological abnormalities. Obesity is one of the greatest causes of risk factors for several chronic diseases, morbidity and mortality such as type 2 diabetes mellitus (DM-T2), dyslipidemias cardiovascular disease (myocardial infarction, stroke), non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea (OSA), osteoarthritis, infertility and development of tumors, among others (3,4).

It is worth noting that in obesity, and especially visceral obesity, adipose tissue (adipocytes, endothelial cells, fibroblast, macrophages) is associated with the release of adipokines (adiponectin, leptin, resistin, visfatin) and proinflammatory cytokines such as tumor-necrosis factor (TNF-α), interleukin-6 (IL-6) and interleukin-12 (IL-12). Furthermore, mediators of clotting such as plaminogen-activator inhibitor type 1 (PAI-1), which is related to insulin resistance, diabetes, atherosclerosis and cardiovascular complications, are also released. However, the impact of all these factors is beyond the scope of the present article.

Evidence shows that the systemic "sterile" inflammatory response that affects certain tissues (adipose tissue, liver, pancreas and heart muscle) is mediated by the stimula-

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tion of the innate immune system by molecular patterns associated with tissue damage (DAMPs) (hypoxia, rough endoplasmic reticulum stress) (5) (Fig. 1). Hypoxia, cellular stress and necrosis promote the activation of macrophages that initiate adipose tissue inflammation. Recently, it has been reported that bariatric surgery causes remission of the inflammatory response (6).

One of the most novel and promising findings has been the relationship between dysbiosis of the microbiota with obesity, DM-T2, and NAFLD. This confirms the participation of the immune system (innate and acquired) with metabolic disorders (bacterial translocation) (7). Zhang et al. reported that Roux-en-Y gastric bypass surgery produced a change in the composition of the microbiota in comparison with obese subjects (8). Due to limitations of space, we remit the reader to a recent review for more detailed information (9).

The most widely accepted parameter to define and classify overweight and obesity is body mass index (BMI), defined as weight in kilograms divided by the square of the height in meters. A BMI of 25.0-29.9 kg/m^2 is considered as overweight; between 30 to 35 kg/m^2, as obesity (Class I); 35.0-39.9 kg/m^2, morbid obesity (class II); and 40.0-44.9 kg/m^2, super-obesity (Class III).

Other clinical parameters with prognostic value include an increase in waist circumference (≥ 102 cm for males and ≥ 88 cm for females), the volume of intra-abdominal visceral fat, thickening of the intima media of the carotid and markers of endothelial dysfunction. All should be included in the assessment of an obese patient (3,10). Obesity is of particular interest for gastroenterologists and surgeons for several reasons:

1. Obesity is associated with multiple digestive disorders: gastro esophageal reflux (GERD), NAFLD, non-alcoholic steatohepatitis (NASH), cirrhosis, hepatocellular carcinoma, gastric adenocarcinoma, diverticular disease, polyps, colon cancer, acute pancreatitis, pancreatic cancer and lithiasis (11).
2. Bariatric-metabolic surgery (BMS) is the safest, most effective and long-lasting treatment to reduce overweight and fat excess and reverse the comorbidities associated with obesity such as DM-T2, hypertension, dyslipidemia, atherosclerosis, NAFLD. It also increases life expectancy (3,12,13).
3. BMS is the most frequent intra-abdominal surgical procedure after laparoscopic cholecystectomy. It represents an anatomical and physiologic reconfiguration of the digestive tract with adverse effects and complications. These are both acute and chronic, which require the intervention of gastroenterologists (vitamin malabsorption, dumping syndrome, GERD, endoluminal stenosis, food intolerance, early satiety, postprandial abdominal fullness and bloating). They demand a rapid diagnosis and knowledge of the physiological mechanisms of these techniques (3,7,13).
4. In 2004, bariatric-metabolic endoscopy (BME) was introduced in the multi-disciplinary treatment of obesity, and in 2017 more than 14,725 endoluminal procedures had been performed (14,15). Similarly, the anatomic remodeling caused by surgery poses a challenge for endoscopists when such procedures are required.
5. The gastrointestinal tract is the largest endocrine (enteroendocrine cells [EEC]) and immune organ in the body. Since the description of secretin by Bayliss and Starling in 1902, more than 30 gastrointestinal neuropeptides have been identified which regulate appetite, food intake and energy balance (16,17).

The aim of this review is to briefly describe the physiologic mechanisms induced by BMS in the treatment of obesity and DM-T2.

The multiple surgical techniques can be classified into three groups: a) restrictive techniques in which the gastric capacity is reduced (examples would be adjustable gastric banding [AGB] and vertical tubular gastrectomy or "sleeve" gastrectomy [SG], which is currently the most widely performed technique in 47 % of cases); b) purely malabsorptive techniques in which distal intestinal diversion is performed (biliopancreatic diversion with duodenal switch [BPD-DS]; 1.1 % of cases); and c) mixed techniques in which the restrictive and malabsorptive components are combined such as Roux-en-Y gastric bypass (RYGBP, 46 % of worldwide procedures), biliopancreatic diversion (BPD) and one anastomosis gastric bypass or mini-gastric bypass (MGB/OAGB). The order of effectiveness for weight loss and diabetes improvement is BPD > RYGBP > SGS > AGB. Figures 2 and 3 show the most frequently used techniques (18).

It is worth highlighting that this type of surgery is termed bariatric (from "baros" meaning weight) and metabolic surgery. This is due to the fact that, apart from weight loss, an early remission of DM-T2 was observed in the first days of the postoperative period, both in restrictive and mixed models. Years later, the "incretins" and their role in the regulation of energy metabolism were identified such as glucagon-like peptide 1 (GLP-1), glucagon-like peptide-2 (GLP-2), glucose-dependent insulinotropic polypeptide (GIP), ghrelin (GR) and peptide tyrosine-tyrosine (PYY). Their role in the regulation of energy metabolism was also determined, thus confirming the metabolic effect of the surgery (7).

Generally speaking, the effects of BMS can be classified into three groups: a) those which are independent of the weight loss and result from the physiologic consequences of the anatomical and physiologic reconfiguration caused by surgery; b) those associated with the weight loss; and c) those caused by changes occurring within the adipose tissue (3).

Here we will briefly describe the effect that is independent of weight loss and those secondary to the anatomical reconfiguration. These have highlighted the involvement of the gastro-entero-insular axis in the regulation of energy metabolism and the resolution of comorbidities. Furthermore, these physiologic changes have served as the foundation for endoluminal prototype design (EndoBarrier®, Gelesis 100, duodenal mucosal resurfacing) (14,15).

GLUCAGON-LIKE PEPTIDE-1 (GLP-1)

As mentioned previously, one of the most striking effects of BMS is the early resolution (during the first days of the postoperative period) of DM-T2. Especially with the techniques that exclude duodenal transit (RYGB, biliopancreatic diversion with or without duodenal switch and OAGB) or those in which the digestive transit is accelerated, as in SG (3,16).

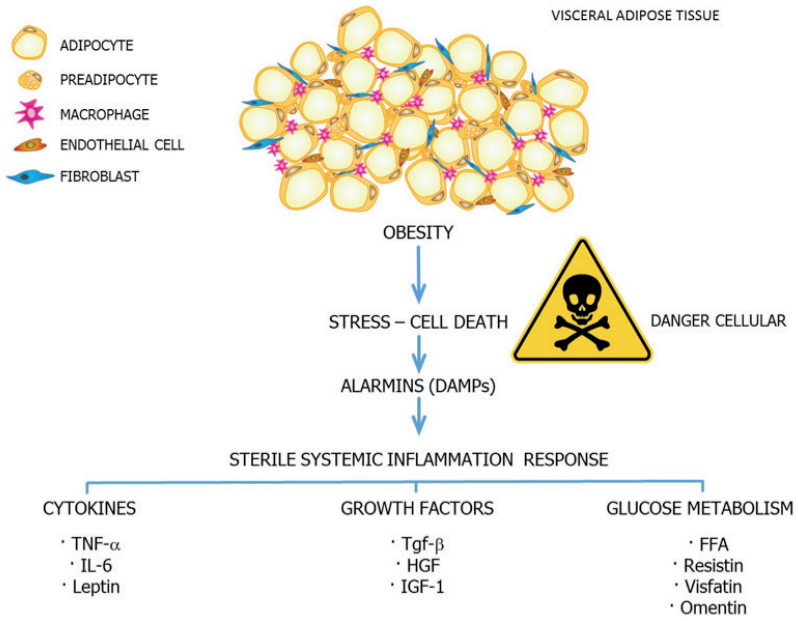

Fig. 1. *Schematic representation of the immunometabolic response in obesity. Obesity leads to the induction of inflammatory signaling pathways. TNF-α: tumor necrosis factor-α; IL-6: interleukin-6; TGF-β: transforming growth factor-β; IGF-1: insulin growth factor; DAMPs: damage associated molecular patterns.*

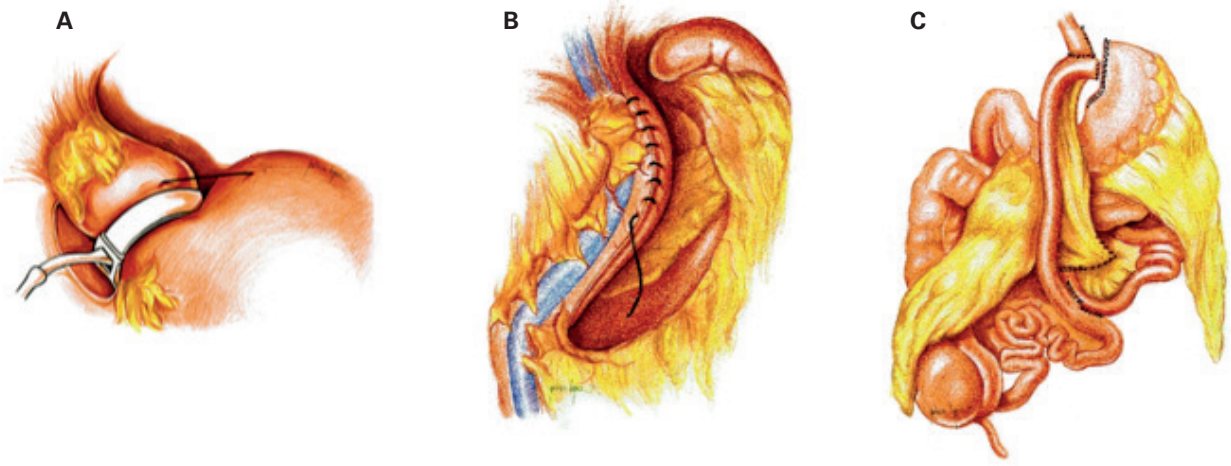

Fig. 2. *The most common bariatric surgical procedures. A. Adjustable gastric banding. B. Sleeve gastrectomy. C. Roux-en-Y gastric bypass. Adapted from John L. Cameron and C. Sandone.*

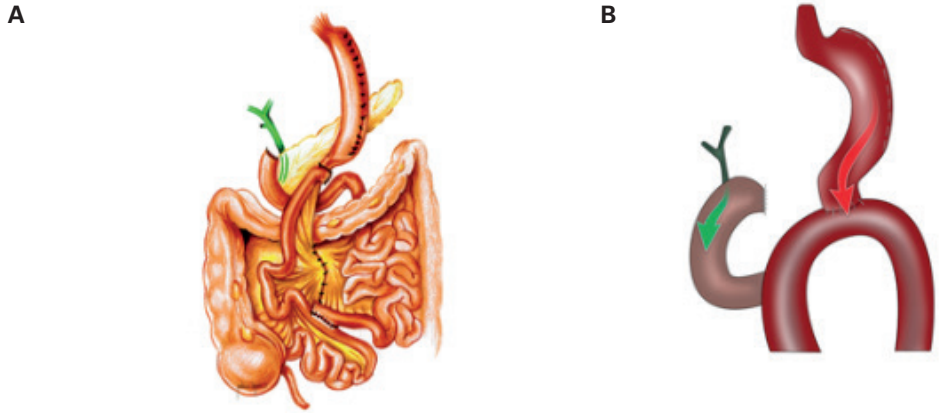

Fig. 3. *A. Duodenal switch (adapted from John L. Cameron and C. Sandone). B. Mini gastric bypass-one anastomosis gastric bypass.*

The incretin effect of the surgery is due to the release of glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide by the EEC of the intestine. The rapid arrival of macronutrients to the proximal and distal intestine stimulates the secretion of GLP-1 and GIP in enteroendocrines K and L cells (19).

GLP-1 has other pleiotropic effects related to DM-T1. It stimulates the secretion of insulin, increases the number and mass of pancreatic islets and inhibits apoptosis of B cells. It is worth noting that pancreatic functional reserve is the factor that best predicts the resolution of DM-T2. Furthermore, it is the basis for widening the indications for surgery to obese and prediabetic patients and for not delaying surgery until the endocrine pancreas is "exhausted", as the outcome would be worse. This trend represents a challenge for health systems as limited resources for this population have to be prioritized (3).

It has already been mentioned that the benefits of BMS are much greater than diet or life style changes for the resolution or control of DM-T2 (75-80 %) (12). In addition to the endocrine response of the pancreas, other adjuvant mechanisms intervene over the long-term in the resolution of DM-T2, such as calorie restriction and weight loss (3). Other studies have also reported hyperplasia of all the layers of the intestinal wall, increase in L cells and an increase in glucose metabolism following RYBP (7). Furthermore, bariatric-metabolic surgery (SG, RYGB and OAGB) stimulates the release of anorexigenic hormones such as GLP-1, peptide YY and oxyntomodulin. These cause a sensation of early satiety and reduce calorie intake (19).

GHRELIN (GH)

Ghrelin is a 28 aminoacid polypeptide that is synthesized in the endocrine cells of the oxyntic glands of the gastric fundus. It exerts central (in the hypothalamus) and peripheral effects, stimulating appetite and food intake with the subsequent increase in body weight and adipose tissue, and is known as the "hunger hormone" (20).

The effects of a restrictive technique such as gastric banding on ghrelin levels are controversial. Some studies have reported a decrease in ghrelin levels, while most have observed an increase in the levels of this hormone with a prolonged follow-up (six months to four years). These changes in ghrelin have been linked to weight loss and not to a direct effect of AGB, which could explain the relapses and loss of efficacy of AGB in the long term. In contrast, the main source of ghrelin is resected (the gastric fundus) in a vertical sleeve gastrectomy and a reduction in the baseline and postprandial levels of ghrelin has been reported (21).

Reported outcomes have been contradictory with regard to the effect of RYGBP. These were related to the specific patient factors (BMI, preoperative severity of the DM-T2) and the surgical technique used, such as size and orientation of the residual gastric reservoir and the length of the loop (7). Our group has reported reductions in ghrelin levels but this depended on the exclusion of the fundus and the lack of contact of macronutrients with oxyntic cells (21).

PEPTIDE YY (PYY)

Another of the gut hormones involved in the "metabolic" effect of bariatric-metabolic surgery is the peptide tyrosine-tyrosine (PYY) (22). PYY was first isolated in 1982 and is synthesized in enteroendocrine L cells and α and δ pancreatic cells (22). Two endogenous forms have been identified, PYY_{1-36} and PYY_{3-36}, with different functions. PYY levels fall when fasting and increase with food intake, depending on the composition of the macronutrients. It has an anorexigenic and regulating effect on energy metabolism. As is the case with other incretins such as GL-P1 and BYP-GP, SG leads to an early and lasting PYY release (> 12 months) of PYY which is associated with the rapid arrival of undigested food in the intestine (22).

It is striking that these surgical techniques exert a much stronger stimulus on the release of PYY than calorie restriction (1,300-1,800 kcal/day) or gastric banding. This explains why surgery yields better results than dieting or physical exercise. Furthermore, it has been reported that PYY_{3-36} exerts a synergistic effect with GL-P1 on insulin secretion, improving glucose tolerance (22). Over the last decade, the search for drugs that are PYY agonists has intensified.

CHANGES IN EATING HABITS

Beneficial changes have been reported with regard to food intake and food preferences in RYGB. A reduction in food intake, an aversion to fats and carbohydrate-rich foods and a preference for fruits and vegetables have been reported. In one study, 65 % of patients undergoing RYGP experienced a reduced taste for sweet foods, whereas 62 % of patients undergoing AGB reported an increased taste for these foods (23). Overall, 82 % of patients undergoing RYGB and 45 % receiving AGB reported changes in taste.

Studies using functional magnetic resonance imaging (fMRI) have confirmed that RYGBP induces changes in the cerebral circuits related to the "reward" system and the mesolimbic pathways related to food addiction. In general, RYGBP is more effective than AGB in reducing the intake of fats and stimulating the consumption of fruits and vegetables. Although at present there are still few studies on sleeve gastrectomy, it appears to have the same effect as RYGBP (3,7,19).

FOOD INTOLERANCE

Apart from the changes mentioned above, bariatric-metabolic surgery causes a series of symptoms and syndromes inherent to the anatomical reconfiguration. These include postprandial fullness, nausea, vomiting and dumping syndrome, all of which are important in long-term outcomes. Patients adapt better over time with the mixed procedures (RYGBP, MGBP, OMGB) and with SG than with adjustable gastric banding (24).

ASSESSMENT OF OUTCOMES AND FUTURE PROSPECTS

The reported efficacy of BMS should be refined by means of the implementation of predictive parameters (to gauge response to treatment), which would allow a better identification and selection of patients for BMS or bariatric endoscopy (3). The body mass index does not discriminate between different degrees of adiposity, insulin reserve or cardiovascular risk factors (10). Currently, there exist methods to evaluate body composition. This allows surgical indications to be individualized, outcomes to be assessed more accurately, and more personalized care to be offered based on the physiologic parameters of patients with other diseases such as breast and colon cancer (25). This also applies to the better identification of the obesity phenotypes with metabolically healthy obesity, with comparable adverse cardiometabolic profiles to patients with metabolically altered obesity (25).

In line with this, some prognostic scales such as the Diarem Score or the Edmonton Obesity Staging System (EOSS) have been developed, which allow comorbidities and functional status to be evaluated. This "holistic" vision of obesity should be incorporated into the practice of both gastroenterologists and surgeons, so that better long-term results with lower levels of morbidity can be obtained (3).

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